DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
Center for Biologics Evaluation and Resear
1401 Rockville Pike
Rockville MD 20852-1448

SEP 13 1999

CBER-99-23

WARNING LETTER

Certified Mail
Return Receipt Requested

John Buechner, Ph.D.
President
University of Colorado
4001 Discovery Lane, Suite 230
Boulder, Colorado 80303

Dear Dr. Buechner:

Between April 5 and 15, 1999, Ms. Teena Aiken and Ms. Deborah Hammond, investigators with the Denver District Office of the Food and Drug Administration (FDA), conducted an inspection of Colorado Multiple Institutional Review Board (COMIRB). The purpose of this inspection was to determine whether your procedures for the protection of human subjects complied with Title 21, Code of Federal Regulations, Parts 50 and 56 [21 CFR 50 and 56]. This inspection was also to confirm that adequate correction of the violations noted during the inspection conducted between February 19 and March 1, 1997, had been made.

A copy of the Inspectional Observations listed on the FDA Form 483 left with the chairman of the COMIRB, Dr. Prochazka, at the conclusion of the April 1999 inspection is enclosed (enclosure #1). The Agency has reviewed the documents and records relating to the COMIRB's responsibilities for the protection of subjects of research contained in the inspection report, and the objectionable conditions and practices listed on the FDA Form 483. Based on our review, we have determined that the COMIRB has violated applicable federal regulations contained in 21 CFR 56. The inspection report indicates that the COMIRB has failed to adequately correct several of the violations noted during the FDA inspection conducted in 1997, as described on the FDA Form 483 issued at the close of that inspection (enclosure #2).

The violations cited during the April 1999 inspection are discussed below and are not intended to be an all inclusive list of the deficiencies in your IRB operation. The applicable provisions of the CFR are cited for each violation.

1. Failure to conduct adequate continuing review of research. [21 CFR 56.109(f)]

During the inspection conducted in 1997, the continuing review of studies was found to be severely inadequate with approximately 758 studies overdue for continuing review. Deficiencies noted during that inspection included a lack of written procedures for conducting continuing review and determining which projects require review more frequently than annually, and, no mechanism to track studies which required review more often than annually. The current inspection revealed that although a new database was implemented to identify all studies requiring continuing review at any frequency and that written standard operating procedures (SOPs) were developed, discrepancies in study files and the database, and failure to adequately review continuing review reports or to act upon the report information, indicate that the continuing review of research is inadequate. This is evidenced by the following:

a. Employees have not been fully trained in the use of the database. Employees were not able to sort or print certain databases and did not know what all the database fields were even though they were responsible for entering data into those fields. It was necessary to utilize a former employee to obtain printouts of open and closed studies.

b. During the inspection, the database and files were compared for accuracy and many examples were noted which indicated that both the files and database contain errors that affect adequate continuing review. Examples include: study 95-286 which was misfiled under the wrong study number and did not appear to have had any continuing review; studies for principal investigator —— . which were in a miscellaneous file but did not show up on the database; and study 85-139 for which the database screen was lacking entries including that for the future action date which would affect alerting the COMIRB that a continuing review was due.

c. The review of continuing review reports is inadequate to address enrollment discrepancies. During the inspection, it was noted that the COMIRB staff are evaluating only discrepancies in number of subjects enrolled in studies reported the previous year, however, discrepancies in enrollment for an entire study are not evaluated. Although the database lists the projected number of subjects to be enrolled in a study, this information is not later reviewed to determine if the investigator is over-enrolling subjects. In some cases, a discrepancy was noted by the COMIRB staff and an explanation requested, however, the continuing reviews were approved for another year without taking the receipt of a response into consideration.

Examples include study 94-597 which had 0 subjects enrolled in 1995, 8 added in 1996, and 13 added in 1997 for a total of 21 enrolled, however, the investigator reported 32 enrolled in 1997. In 1998, the investigator reported that 0 subjects had been added but that a total of 35 subjects were enrolled. In 1999, no new subjects were reported and the total enrollment was reported as 33. The COMIRB requested an explanation for only the current year's discrepancy of 33 versus 35 subjects. In addition, the chairperson approved the study for another year prior to the request for an explanation of the discrepancy. In study 96-210, the 3/10/97 continuing review reported that 7 subjects had been enrolled. In 1998, the clinical investigator stated that 12 subjects had been enrolled in the last year for a total of 10 subjects. This discrepancy was not noted and re-approval was granted. In 1999, the report stated that 6 more subjects had been enrolled since the last report, for a total of 26. The COMIRB noted the discrepancy in the number of subjects reported in 1999 from the previous year and requested an explanation of the discrepancy, however, the chairperson signed the continuing review as approved for another year prior to the request for an explanation of the discrepancy.

d. Records do not indicate that adverse events were reviewed by the IRB.

e. For study 96-329, the FDA's inspection noted that the "COMIRB Protocol Continuing Review Form" question number 8, which asks if consent/assent forms are still acceptable, was not answered. Although a letter was sent to the principal investigator regarding discrepancies in the number of subjects enrolled, the issue regarding the consent form was not addressed.

f. For study 97-149, the continuing review form indicated that the principal investigator had changed, however, the change in principal investigator was not corrected by the COMIRB in the database and the form was not signed by the current principal investigator.

g. During the inspection, records for the study "[redacted]" were examined. This study had been ongoing for 24 years, having been approved in 1974 and closed in 1999. There was no evidence that the COMIRB ever re-evaluated this study to ensure consideration of current technology or changes in the COMIRB procedures for approval or review.

Continuing IRB review of research must be substantive and meaningful. The purpose of continuing review is to review the progress of the entire study, not just changes in it. The file should be reviewed examining, at a minimum, any previous progress reports including: the number of subjects accrued; a summary

description of subject experiences (benefits, adverse reactions); numbers of withdrawals from the research; reasons for withdrawals; complaints about the research; research results obtained thus far; a current risk-benefit assessment based on study results; and any new information since the IRB's last review. The IRB should obtain a copy of the current consent document and determine whether the information contained in it is still accurate and complete, including whether new information that may have been obtained during the course of the study needs to be added.

Continuing review of a study may not be conducted through an expedited review procedure, unless the study was eligible for, and initially reviewed by an expedited review procedure, or the study has changed such that the only activities remaining are eligible for expedited review.

2. **Failure to prepare and follow detailed written procedures for conducting the review of research, including periodic review. [21 CFR 56.108(a),(b), and 56.115(a)(6)]**

   a. Complete SOPs for the use and maintenance of the database have not been written. Written instructions were available for operating the database regarding field information and continuing review, however, these instructions have not been incorporated into the COMIRB SOP document entitled "Policies and Procedures."

   b. The completion of attendance sheets for meetings is not described in the SOPs. The current employee responsible for filling out this sheet indicated that she did not know what the "rev" column was supposed to be used for but she uses it to identify members who have studies to review. A former employee used the "rev" column to indicate a member who was not present but was supposed to present a study and had submitted comments for the meeting.

   c. Records indicate that procedures for continuing review remain inadequate. They do not fully address what staff employees are to review or how to resolve discrepancies when continuing review deviations are found. Examples noted include a lack of procedures to handle discrepancies in the numbers of cited adverse events and missing signatures.

   d. The COMIRB "Instructions for Clinical Investigators" SOP 7.2 states that failure to respond to continuing review requests will result in suspension of approval. However, termination of approval is not addressed nor does the SOP delineate the current procedures followed for suspension or termination. In addition, SOPs do not address interim periods in the continuing review process when a principal investigator has responded to

the COMIRB questions and the COMIRB is corresponding with the principal investigator. Studies may be terminated and then reopened following a complaint by the principal investigator that issues are still under discussion with the COMIRB for resolution. Neither of the two administrative support staff employees checked whether there was a response letter before sending a suspension or termination letter.

e. Studies are reinstated without consistent criteria or SOPs for reinstatement.

f. SOPs have not been developed to require that the termination status of studies and the reason for termination be entered in the database. However, studies which are terminated may be cited as closed in the database. The actual status of some studies cited as closed in the database could not be determined. For example, the study entitled "[redacted]" was approved in 1974 and may have been terminated on 4/9/99 due to a lack of response to an enrollment deficiency letter. However, the database indicates the study as closed on 4/9/99.

3. **Failure to follow written procedures for ensuring the prompt reporting of any suspension or termination of IRB approval. [21 CFR 56.108(b)(3)]**

The COMIRB does not notify FDA when studies are suspended or terminated due to lack of compliance with IRB requirements. Although the SOPs state that this should be done automatically in any case of suspension or termination of the COMIRB approval, the COMIRB personnel were under the impression that they only need notify FDA of termination if there was a safety issue.

4. **Failure to prepare and maintain adequate documentation of IRB activities including continuing review. [21 CFR 56.115(a)(2), (3), and (4)]**

a. The new COMIRB database, which is utilized by the COMIRB to identify all studies requiring continuing review, has never been audited against actual files to assure accuracy. Some studies were identified during the inspection that do not appear in the database. In addition, inadequate documentation and/or many data discrepancies were noted in the files and database. Updating procedures for the database only included checking files that showed up on the database and only the database was evaluated for overdue continuing reviews.

Many discrepancies were noted in and between the files and the database. For example, study 95-286 was incorrectly filed as study 95-268 and was not entered in the database. It does not appear that any continuing review of this study occurred. The study entitled "[redacted]

" is filed in an open file but the database shows the study as closed 3/8/99. Numerous studies for principal investigator —— were found in a miscellaneous file but were not entered in the database. An accurate list of all terminated or suspended studies could not be provided by sorting the database. A database list indicating that 43 studies had been terminated was provided during the inspection, however, when this was compared with termination letters, it was noted that at least 2 terminated studies, 95-466 and 96-245, did not appear on the database list and that the list did not include suspended studies.

b. Meeting minutes include undated, handwritten entries which are not initialed and do not elaborate on serious issues discussed during meetings such as resolution of suspension notices. During the 8/14/98 meeting, study 96-522 was listed on the agenda as an urgent item regarding suspension of a study conducted by Dr. —— who is a COMIRB member. There are no meeting minutes stating what the suspension notice was about or how it was resolved.

c. During the inspection conducted in 1997, it was noted that meeting minutes lacked a record of attendance and vote, and that meeting minutes did not indicate whether members participated in the deliberation of their own studies. The current inspection noted that there continues to be a lack of documentation that members with conflicts of interest abstain from initial or continuing review of their studies. In addition, meeting minutes do not document whether guest principal investigators are dismissed when the COMIRB votes on the guest's study.

Dr. —— a member of the committee, listed a conflict of interest regarding studies conducted by the principal investigator for study 98-536, however, there is no documentation that he was dismissed during the 8/14/98 vote on this protocol. Study file notes for study 98-438 indicate that Dr. —— a committee member and co-investigator, did not vote on the study, however, there is nothing in the 8/14/98 meeting minutes to indicate that he did not vote nor do the minutes indicate that he was a co-investigator. The COMIRB document listing the expertise and conflicts of interest of members indicates that the IRB member is not able to vote on —— studies but does not list —— members. There is no documentation in the 8/14/98 meeting minutes that Dr. —— was dismissed during a vote on the review of study 96-522 for which she is the principal investigator. Study 98-742 was reviewed for approval during the 1/8/99 meeting. The principal investigator for this study is listed as Dr. ——. A handwritten entry in the meeting minutes states that Dr. —— presented the study, however, he is not recorded in the meeting minutes as a guest. Although a box is checked in the meeting minutes indicating that guest participation is for discussion only, the check

is typed in before the meeting occurs. The meeting minutes do not document whether the principal investigator was dismissed when the COMIRB voted on the study.

d. Study 595-9601 should have undergone full committee review and approval, however, meeting minutes do not document that this occurred. It appears that the study underwent expedited review because the primary reviewer was not present at the meeting. The meeting minutes do not indicate whether it was reassigned to another member. There were no comments in the meeting minutes other than that the reviewer was "out" and no notation that the protocol was approved or postponed. The record indicates that the study was approved prior to the next IRB meeting.

Currently, the COMIRB is responsible for about —— open protocols. The COMIRB meets twice a month for three hours. ——— new studies are approved at every meeting and review is conducted on numerous items such as continuing review, amendments, and adverse events. During the inspection it was noted that stacks of paperwork were not filed, the voice mail was full preventing principal investigators from leaving messages and, principal investigators complained that their phone calls were not returned in a timely manner. As noted above, the new database had not been audited to assure its validity, and, functions and operations of the IRB are inadequate to ensure adequate continuing review. It was noted during the inspection that in the next 2-3 years, ———————————— , the University of Colorado intends to ———————————————————— . Central to the failure of the IRB to meet its obligations and responsibilities appears to be the lack of sufficient support staff and the proper training of this staff. The two support staff employees were not sure what their duties and responsibilities entailed and were not proficient in using the database.

We have little confidence that meaningful and adequate deliberation of review of research can occur during convened meetings of the COMIRB as it now operates to provide for the oversight required for the protection of human subjects of research.

Administrative Restrictions

The seriousness of these deviations requires that FDA implement administrative action, per 21 CFR 56, to assure compliance with the regulations governing IRBs. For this reason, in accordance with 21 CFR 56.120(b)(1) and (2), and effective immediately,

- **no new studies** that are subject to 21 CFR Parts 50 and 56 are to be approved by your IRB, and

- **no new subjects** are to be admitted to ongoing studies that are subject to 21 CFR Parts 50 and 56 until you have received notification from this office that

adequate corrections have been made.

These restrictions do not relieve the IRB from receiving and reacting to proposed amendments, reports of unexpected and serious reactions, and routine progress reports from ongoing studies.

Please inform this office, in writing, within fifteen (15) working days from the date of receipt of this letter, of the actions you have taken or plan to take to bring the procedures of your IRB into compliance with the applicable regulations. Please include a copy of any revised documents, such as written procedures, with your response. Any plan of action should include projected completion dates for each action to be accomplished. In addition, all institutions participating in the COMIRB consortium should be notified in writing of these restrictions and copies of the notifications should be submitted. We will review your response and determine whether the actions are adequate to permit the IRB to resume unrestricted activities. Your failure to adequately respond to this letter may result in further administrative actions against your IRB, as authorized by 21 CFR 56.120 and 56.121. These actions may include, but are not limited to, the termination of all ongoing studies approved by your IRB and the initiation of regulatory proceedings for disqualification of your IRB.

Please send your written response to:

Patricia E. Hasemann (HFM-650)
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Food and Drug Administration
1401 Rockville Pike
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Telephone: (301) 827-6337.

Sincerely,

for Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research

ENCLOSURES
1. 1999 FDA Form 483
2. 1997 FDA Form 483